UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,159	08/15/2001	Tania Kastelic	1556.0290000	9266

7590 06/17/2003

Sterne Kessler
Goldstein & Fox
Suite 600
1100 New York Avenue NW
Washington, DC 20005-3934

EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/869,159	Applicant(s) KASTELIC ET AL.	
	Examiner Celine X Qian	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-17* is/are rejected.

7)☒ Claim(s) *10 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1 and 3-17 are pending in the application. Claim 2 is cancelled.

This Office Action is in response to the Amendment filed on 1/28/03 and 4/2/03.

Response to Amendment

Acknowledgment is made of Applicants' submission of sequence listing, and the application is in sequence compliance.

The rejection of claim 11 under 35 U.S.C. 101 has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 4-9 and 12-14 under 35 U.S.C.112 1st paragraph has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 1, 3-14 under 35 U.S.C.112 2nd paragraph has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 1 and 3 under 35 U.S.C. 102 (b) has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claim 4 under 35 U.S.C. 103 (a) has been withdrawn in light of Applicants' amendment of the claims.

Claim 11 is rejected under 35 U.S.C. 112 1st paragraph for reasons discussed below.

Claims 4, 5, 8-14 and newly added claims 16-17 are rejected under 35 U.S.C. 112 2nd paragraph for reasons discussed below.

Claims 4-7, 10, 12-14 and newly added claims 16-17 are rejected under 35 U.S.C.102 (b) for reasons discussed below.

Claims 1, 3-14 and newly added claims 15-17 are rejected under 35 U.S.C.103 (a) for reasons discussed below.

Claims 10 and 11 are objected to for reasons discussed below.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

The nature of the invention is a method of treating or preventing a disease that is associated with inappropriate mRNA stabilization, accumulation and undesirable protein

expression by administering a compound that affects mRNA stability or induce mRNA degradation.

The breadth of the claim is very broad. The claim encompasses a method of preventing or treating any type of disease that is associated with inappropriate mRNA stabilization, accumulation and undesirable protein expression by administering a compound that affects mRNA stability or induce mRNA degradation.

The teaching of the specification is limited. The specification does not teach any disease or medical condition that is associated with mRNA stabilization or accumulation. The specification only discloses compounds such as radicicol analogue A that destabilizes mRNA through AU rich motifs located within 3' UTR of IL-1β. The specification does not disclose whether any type of disease associated with mRNA stabilization may be prevented or treated with these compounds. Without teaching from the specification, one skilled in the art would have to turn to prior art for guidance of practice the method as claimed.

The state of art at the time of filing is silent on what kind of disease or medical condition is associated with inappropriate mRNA stabilization and accumulation. Therefore, whether compounds that destabilize mRNA can prevent or treat such unknown disease is unpredictable. Further, even if the diseases are identified, whether compounds that destabilizes mRNA can treat or prevent such diseases is still unpredictable because those compounds identified by screening in an *in vitro* expression system would destabilize all endogenous genes comprising mRNA instability sequence. As such, the overall effect of these compounds is unpredictable.

The claim also encompasses treating diseases associated with undesirable protein expression. There are many diseases involve undesirable protein expression, for example,

oncogene expression in cancer. However, neither prior art or the specification teaches whether the compound destabilizes mRNA can prevent or treat cancer. Therefore, without teaching from the specification and prior art, one skilled in the art would have engage in undue experimentation to determine 1) what kind of disease is associated with mRNA instability; 2) whether compound induce mRNA instability *in vitro* can treat or prevent such disease. Consequently, the claim is not enabled as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 8-14, 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 4, 5, 12, 13, 16 and 17, the term "substantial part" renders the claim indefinite because it is unclear how big the 3'UTR needs to be to function as an instability sequence.

Regarding claims 4, 5, 8, 9, 11-14, 16 and 17, the word "associated" renders the claims indefinite because it is unclear whether the "5' and 3' UTR" is native to the "gene" or from other genes and operably linked to coding sequence of the recited gene.

Regarding claims 16 and 17, the word "derived" renders the claim indefinite because the nature and number of derivative process is unknown. As such, the metes and bounds of the claim cannot be established.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4-7, 10, 12-14, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Banholzer et al.

The disclosure of Banholzer et al. has been discussed in detail in the previous office action (see page 6). Banholzer et al. further disclose three plasmid constructs pMx-AP-wt IL3, pMx-AP-ΔAUIL3 and pPIL3-AP-wt IL3, which comprise either the LTR promoter or IL3 promoter, an AP reporter gene and either wild type or mutant IL3 3'UTR that comprises the mRNA instability sequence. Applicants point out that Banholzer et al. do not disclose an expression system to detect a protein signal. However, the claims are drawn to an expression system comprising a DNA encoding a protein having a detectable signal. Any protein would have a detectable signal because they can be detected by labeled antibody. Therefore, Banholzer et al. disclose the instantly claimed invention.

Banholzer et al. also disclose rapamycin and FK-506 induces mRNA degradation. As discussed in the previous office action, claims 10, 12-14 are product by process claims which read on the product, in the present instance, a compound which destabilizes mRNA. Absent evidence to the contrary, the method by which the compound is identified does not impart upon said compound a patentable distinction from another such compound. Therefore, Banholzer et al. disclose the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banholzer et al., in view of Zhang et al (1996, BBRC, vol.227, pages 707-711).

The teaching of Banholzer et al. was discussed in the previous office action and above. However, Banholzer et al. do not teach a method of screening compounds that affect mRNA stability by using an expression system comprising a reporter gene, wherein the protein signal is measured to determine whether the test compound affects mRNA stability.

Zhang et al. teach several reporter genes, such as secreted alkaline phosphatase, B-gal, firefly luciferase, CAT and GFP can be used in *in vivo* reporter assays (see page 707, 3rd paragraph). Zhang et al. further teach that GFP is an important reporter because it has advantages over other reporter for not requiring additional cofactors, substrates, or additional gene products. Zhang et al. further teach the generation of a humanized EGFP that has great sensitivity and stability (see bridging paragraph of 708 and 709).

It would have been obvious to one of ordinary skill in the art to develop a method of screening compound that induce mRNA instability by using an expression cassette taught by Banholzer and further attach a GFP reporter gene. One of ordinary skill in the art would have been motivated to do so because the advantages offered by a GFP reporter over measuring

mRNA stability by Northern blot, such as the non-invasive nature of direct measurement of fluorescent intensity. The level of skill in the art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to make an expression cassette comprising a GFP reporter and mRNA instability sequence to screen for compounds that induce mRNA instability. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Claims 8 and 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Danner et al., 1998 (AS4)., in view of Maniatis et al. (1987).

The teachings of Danner et al. and Maniatis et al. were discussed in the previous office action. The reasons for obviousness rejection were also discussed in the previous office action (see page 6 and 7).

Applicants argue that Danner et al. do not teach a vector comprising a gene encoding a protein having a detectable signal, hence Danner et al. is seriously deficient as a primary reference and the invention is not obvious.

This argument has been fully considered but deemed unpersuasive. The claims are drawn to a cell line comprising a first expression cassette comprising a mRNA stability sequence and DNA coding for a protein having a detectable signal, and a second control expression system comprising a reporter gene different than the one in the first expression system but lack mRNA instability sequence, and an assay system comprising said cell line. Danner et al. teach a cell line transfected with a wild type β2AR expression vector, a β-globulin expression vector and a chimeric expression vector comprising β-globulin and 3'UTR of β2AR (either with or without

mRNA instability sequence). As discussed above, any protein would have detectable signal because they can be detected by labeled antibody. As such, β2AR and β-globulin are protein with detectable signal. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim Objections

Claims 10 and 11 are objected to as being dependent upon a cancelled base claim (2). Applicant is advised to rewrite the claim in independent form including all of the limitations of (canceled) base claim (2).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
June 13, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER